Usefulness of Single Fiber EMG for Distinguishing Neuromuscular from Other Causes of Ocular Muscle Weakness

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Abstract: Consecutive patients (n = 114), who had single fiber electromyography of the frontalis muscles for symptoms suggestive of ocular myasthenia gravis, were followed up for a mean of 14 months (3-64 mos). At follow up, based on strict criteria, 23 patients were classified as having ocular myasthenia gravis, 8 patients were diagnosed as having mitochondrial myopathy or oculopharyngeal dystrophy, 18 patients were found to have other diseases and 65 patients remained without a definite diagnosis. The single fiber electromyography data of these patients were then reviewed. The patients with ocular myasthenia gravis had, on average, more than 7/20 single fiber pairs with jitter > 45 μs and mean jitter of 56 μs. The 8 patients with mitochondrial myopathy or oculopharyngeal dystrophy had an average of 5/20 single fiber pairs with jitter > 45 μs and a mean jittter of 52 μs and could not be separated from the group with ocular myasthenia gravis on the basis of the single fiber electromyography results. The 18 patients with definite other diagnosis had an average of less than 1/20 single fiber pair with jitter > 45 μs and a mean jitter of 25 μs. This group could be clearly separated from the group with ocular myasthenia gravis. We conclude that single fiber electromyelography is useful in the separation of ocular myasthenia gravis from other causes of oculomotor weakness except mitochondrial myopathy and oculopharyngeal dystrophy.

Résumé: Utilité de l'EMG de fibres uniques pour distinguer l'origine neuromusculaire d'autres causes de faiblesse des muscles oculaires. Nous avons suivi pendant 3 à 64 mois (moyenne de 14 mois) des patients consécutifs (n = 114) qui ont eu un électromyogramme de fibres uniques des muscles frontaux (EMGFUF) à cause de symptômes suggestifs d'une myasthénie grave (MG) oculaire. Au cours du suivi, 23 patients ont été classifiés comme étant atteints de MG oculaire, 8 patients ont eu un diagnostic de myopathie mitochondriale ou de dystrophie oculopharyngée, 18 patients étaient atteints d'autres maladies et 65 patients n'ont pas reçu de diagnostic définitif. Nous avons revisé les données de l'EMGFUF de ces patients. Les patients avec MG oculaire avaient, en moyenne, plus de 7/20 paires de fibres uniques avec des excitations > 45 μs et une moyenne de 56 μs. Les 8 patients atteints de myopathie mitochondriale ou de dystrophie oculopharyngée avaient en moyenne de 5/20 paires de fibres uniques avec des excitations > 45 μs et une moyenne d'excitations de 52 μs et ne pouvaient pas être distingués du groupe avec MG oculaire à partir des résultats de l'EMGFUF. Les 18 patients avec un diagnostic définitif autre avaient en moyenne moins de 1/20 paire de fibres uniques avec des excitations > 45 μs et une moyenne d'excitations de 25 μs. Ce groupe peut être distingué clairement du groupe de MG oculaire. Nous concluons que l'EMGFUF est utile pour séparer la MG oculaire des autres causes de faiblesse oculomotrice, sauf de la myopathie mitochondriale et de la dystrophie oculopharyngée.

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Single fiber electromyography of the frontalis muscles (SFEMGF) is considered to be the most sensitive laboratory test for ocular myasthenia gravis (MG).[1] The test is reported to be abnormal in 78-86% of patients with ocular MG[2-5] although it was not stated how a final diagnosis of ocular MG was established in these cases. However, SFEMGF is not specific for ocular MG. Using the conventional cut-off criterion of 10% or more single fiber pairs with jitter > 45 μs or of mean jitter > 34 μs, the test was reported to be abnormal in 6 of 32 patients with diseases other than ocular MG.[5] In particular, in patients with mitochondrial myopathy, the test was abnormal in 10/13[6] to 5/5 of patients.[7]

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From previous studies, it was found that the number of abnormal single fiber pairs in patients with MG was usually higher than 10% (25-55%) and the mean jitter was usually higher than 34 μs (41-51 μs).[3-5] In a preliminary report[8] it was suggested that the specificity of SFEMGF and in particular the ability to distinguish ocular MG from mitochondrial myopathy and oculopharyngeal dystrophy might be improved by raising the cut-off criteria to higher values.

This study examines the sensitivity and specificity of SFEMGF for distinguishing ocular MG from other mimicking diseases, particularly mitochondrial myopathy and oculopharyngeal dystrophy. Various cut-off criteria for the number of abnormal single fiber pairs and for the mean jitter are examined in order to define the optimal criteria for such purpose.

Methods

Consecutive patients who were referred to an electromyography laboratory for diagnosis or exclusion of ocular MG during the period from May 1986 to August 1991 were reviewed. The majority of the patients were referred by neurologists or neurophthalmologists. All patients had symptoms and/or signs of muscle weakness in ocular and/or eyelid muscles, with or without additional weakness in other cranial nerve muscles. Patients with limb or trunk weakness were excluded. To be included in the study, a patient had to have a complete SFEMGF study and a follow-up period of at least 3 months.

SFEMGF recordings were made from the voluntarily contracted frontalis muscles on both sides using a standard SFEMG electrode (Teca 909 SF25) and a hard-wired jitter meter (Dantec 15G22). A complete study included the examination of 20 single fiber pairs. At the time of the test, the examiner was unaware of the patient's final diagnosis.

At the time of follow up, the patients' charts were reviewed in detail to determine their final diagnoses. Where the information was incomplete, the referring doctor and/or the patient was contacted for more detailed information.

The final diagnosis was allocated to 1 of the following 4 groups. The definition of each group is as follows:

1. Definite MG. All of the following had to be satisfied.
   - Weakness in extraocular and/or eyelid muscles compatible with a diagnosis of ocular MG.
   - No clinical or laboratory evidence for another condition that could account for the symptoms and signs.
   - Definite improvement agreed to by both the doctor and the patient after treatment with anticholinesterase agents and/or corticosteroids.
   - Maintenance of the improvement for at least 3 months.
2. Mitochondrial myopathy or oculopharyngeal dystrophy.
   - Definite muscle biopsy proof of the condition.
3. Definite other disease. Either or both of the following had to be satisfied.
   - Laboratory proof (e.g., MRI, CT or thyroid function tests) of a condition that could account for the symptoms and signs.
   - Clinical progression with the development of signs definitely ruling out myasthenia gravis (e.g., pupillary abnormalities or involuntary movements).
4. No definite diagnosis.
   - Not fulfilling the criteria for any of the above categories.

Statistics

Student's t-tests were used to assess the differences in the number of abnormal single fiber pairs and mean jitters between each group. An abnormal single fiber pair was defined as a single fiber pair with jitter > 45 μs.

The sensitivity and the specificity of the test were calculated for different cut-off criteria for abnormal single fiber pairs and for mean jitter to generate Receiver Operating Characterisitcs. The sensitivity and the specificity of SFEMGF were defined as follows.

Positive test = a test in which the number of abnormal single fiber pairs or the mean jitter is equal to or higher than the cut-off criterion.

Negative test = a test in which the number of abnormal single fiber pairs or the mean jitter is less than the cut-off criterion.

Sensitivity = the number of patients with definite MG with positive test / the number of patients with definite MG.

Specificity = the number of patients with other diseases with negative test / the number of patients with those diseases.

Results

One hundred and fourteen patients were included in the study; 44 were male and 70 were female. The mean age was 48 years (range 17-80 years). The mean duration of follow-up was 14 months (range 3-64 months). At follow up, 23 patients were classified as definite ocular MG, 8 as mitochondrial myopathy or oculopharyngeal dystrophy, 18 as definite other disease and 65 as no definite diagnosis. The profile of patients in each group is shown in Table 1. The diagnosis in patients with diseases other than ocular MG are shown in Table 2.

The 23 patients classified as definite MG had an average of 7.8/20 abnormal single fiber pairs (range 0-20/20) and a mean jitter of 56.4 μs (range 26-116). Nineteen (83%) had 2/20 or more abnormal single fiber pairs and 16 (70%) had mean jitter greater than 34 μs.

The 8 patients with mitochondrial myopathy or oculopharyngeal dystrophy had an average of 5.4/20 abnormal single fiber pairs and a mean jitter of 51.8 μs. These values were not significantly different from those of the patients with definite ocular

Table 1. Profile of Patients Segregated by Final Diagnosis.

	Final Diagnosis				
	MG	**M/O**	**O**	**N**	**Total**
No.	23	8	18	65	114
Age (years) #	45.7	44.9	43.1	51.1	48.3
Range	20-77	19-72	20-72	17-80	17-80
M:F	9:14	3:5	5:13	27:38	44:70
Follow-up (months) #	11.0	8.1	18.8	15.0	14.3
Range	3-44	3-18	3-36	3-64	3-64
Abnormal Pairs #	7.8	5.4	0.3	3.6	4.0
Mean Jitter (μs) #	56.4	51.8	25.2	41.4	42.6
No. of Blockings #	1.4	0.6	0.1	0.8	0.8

MG = definite ocular myasthenia gravis, M/O = mitochondrial myopathy or oculopharyngeal dystrophy, O = definite other diagnosis, N = no definite diagnosis. No. = number, M = male, F = female. # The value is the mean of that variable. Values for abnormal pairs are the numbers of abnormal single fiber pairs in 20 examined pairs.

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Table 2. Final Diagnosis in Patients with Definite Diagnoses Other than Ocular MG.

Diagnosis	No.	Abnormal Pair (mean)	Mean Jit. (mean)
Group 1	8	5.4	51.8
Mitochondrial myopathy	6	5.3	53.0
Oculopharyngeal dystrophy	2	5.5	48.0
Group 2	18	0.3	25.2
Dysthyroid ophthalmopathy	7	0.4	25.4
Brainstem infarction	4	0.0	24.8
Multiple sclerosis	2	0.0	21.0
Blepharospasm/Meige syndrome	2	1.0	30.5
Orbital pseudotumor	1	0.0	27.0
Horner's syndrome	1	0.0	24.0
Munchaussens' syndrome	1	0.0	22.0
TOTAL	26	1.8	33.3

No. = total number of patients. Mean jit = mean jitter. Values of mean jitter are in microseconds.

MG. Six (75%) of them had 2/20 or more abnormal single fiber pairs and mean jitter greater than 34 µs. The abnormalities in mitochondrial myopathies and in oculopharangeal dystrophy were similar in the two conditions (Table 2).

The 18 patients with definite other diseases had an average of less than 1/20 abnormal single fiber pair and a mean jitter of 25.2 µs. These values are significantly different from the patients with definite MG ($P < 0.01$).

The sensitivity and specificity of SFEMGF were calculated for different cut-off criteria for the number of abnormal single fiber pairs (from 0 to 20) and for mean jitter (from 10 µs to 120 µs). The Receiver Operating Characteristics for both variables were constructed and are shown in Figure 1 and Figure 2. In general, the part of the curve with the maximal sum of sensitivity and specificity represents the optimal cut-off values in differentiating ocular MG from other diseases.

Both figures show that the test cannot discriminate very well between patients with definite ocular MG and patients with mitochondrial myopathy or oculopharyngeal dystrophy. The best simultaneous sensitivity and specificity is obtained with cut-offs of 5/20 abnormal single fiber pairs and a mean jitter of 50 µs. The sum of sensitivity and specificity for these cut-offs are both 1.2. (The best theoretical value for the sum is 2). On the other hand, the test can distinguish clearly between patients with definite ocular MG and patients with definite other disease other than mitochondrial myopathy or oculopharyngeal dystrophy. In this case the best sensitivity and specificity are obtained with cut-offs of 1/20 abnormal single fiber pair and of mean jitter of 30 µs. The sum of sensitivity and specificity for the criterion of abnormal single fiber pairs is 1.76 and that for the criterion of mean jitter is 1.72.

Of the 65 patients in the "no definite diagnosis" group, 30 were suspected of having ocular MG on clinical grounds but had mild symptoms that did not require therapy or that made response to treatment difficult to ascertain, 35 might have had disorders of specific cranial nerves, levator palpebrea dysinsertion, mitochondrial myopathy, dysthyroid ophthalmopathy or other diseases, but definitive proof was lacking. The mean number of abnormal single fiber pairs in the group suspected of having ocular MG was 5.43/20 and the mean jitter was 48.6 µs while

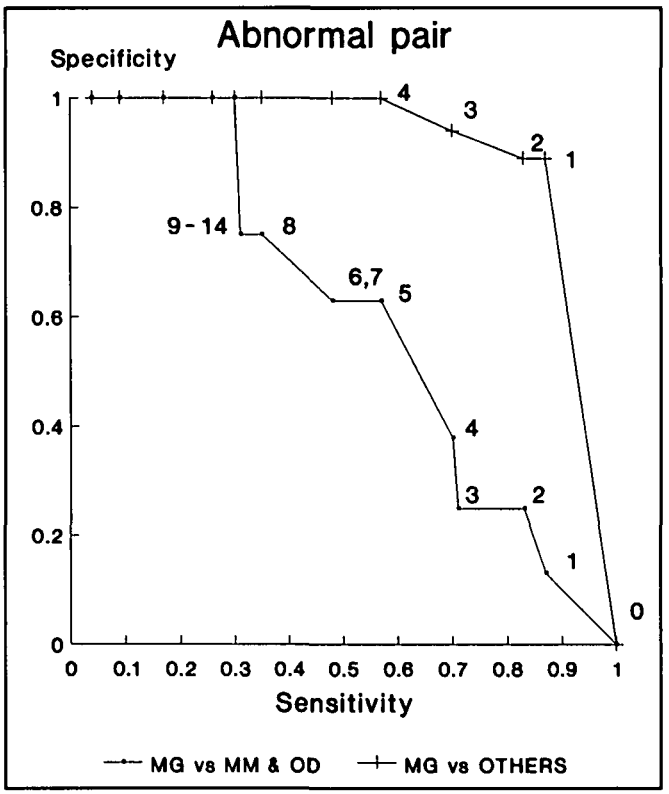

Figure 1: Receiver operating characteristics. MG = ocular myasthenia gravis, MM = mitochondrial myopathy, OD = oculopharyngeal dystrophy. The numbers in the graph are the numbers of abnormal pairs.

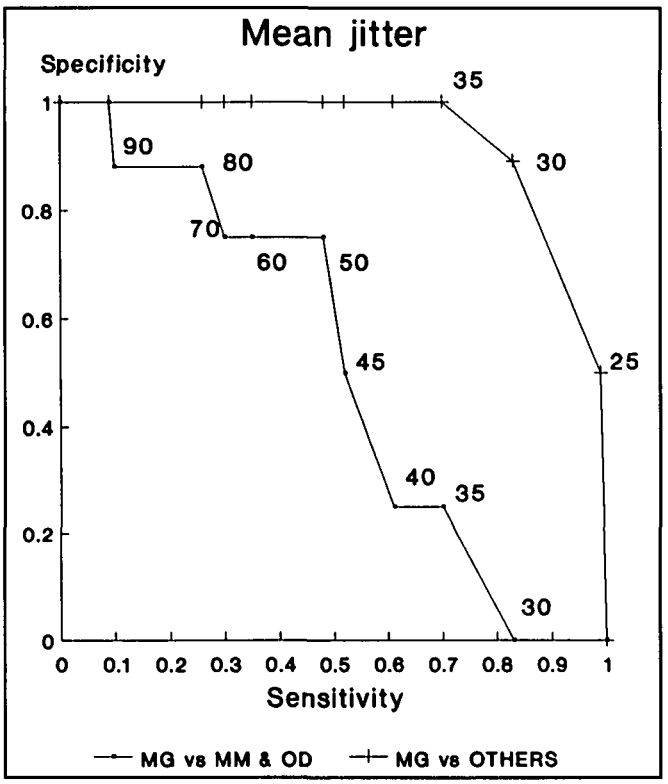

Figure 2: Receiver operating characteristics. MG = ocular myasthenia gravis, MM = mitochondrial myopathy, OD = oculopharyngeal dystrophy. The numbers in the graph are mean jitter values.

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the mean number of abnormal single fiber pairs of the group suspected of having other diseases was 1.97/20 and the mean jitter was 35.3 μs. These two variables are significantly different between the two groups ($p < 0.01$).

Discussion

There is no gold standard for the diagnosis of ocular MG although some consider definite clinically-observed, fatigue-induced paresis of a muscle that is relieved by resting of that muscle to be a diagnostic criterion. In this study, we used compatible clinical features and a definite and sustained response to treatment to establish a diagnosis of ocular MG. Patients classified as definite MG in our study certainly had ocular MG. In this study, SFEMGF was positive in 83% of patients with definite ocular MG when the conventional criterion of 10% or more abnormal single fiber pairs was used. It was positive in 70% of the same patient group when the conventional criterion of mean jitter > 34 μs was used. These figures are comparable to 78-86% found in other studies,[2-5] although the diagnostic criteria in these studies and ours are not exactly the same. Thus about 17% of patients with ocular MG may have normal SFEMGF at these cut-offs.

Our results show that SFEMGF is sensitive and specific in differentiating definite ocular MG from other diseases other than mitochondrial myopathy and oculopharyngeal dystrophy. The optimal criteria for this purpose are 1/20 abnormal single fiber pair (sensitivity = 87% and specificity = 89%) and mean jitter of 30 μs (sensitivity = 83% and specificity = 89%). Both criteria are close to the conventional ones.

The Receiver Operating Characteristics show that SFEMGF is not very helpful in differentiating definite ocular MG from mitochondrial myopathy or oculopharyngeal dystrophy. In our study, 75% of these patients had abnormal tests by the conventional criteria and varying the cut-offs produces little improvement in the combined sensitivity and specificity. The high percentage of abnormal tests in mitochondrial myopathy has been observed previously to be 77%[6] to 100%.[7] There was no previous study of SFEMGF in patients with oculopharyngeal dystrophy but from previous single fiber electromyographic studies in patients with various types of muscular dystrophy, abnormal jitter was often found in these diseases.[9] Abnormal jitter is found in extensor digitorum communis in 63% of patients with ocular MG and 41% of patients with mitochondrial myopathy[6] so it is unlikely that examination of other muscles would help to distinguish these conditions.

We conclude that SFEMGF is sensitive and specific in differentiating definite ocular MG from other diseases apart from mitochondrial myopathy and oculopharyngeal dystrophy. The optimal cut-off criteria for this purpose are 1/20 abnormal single fiber pair and mean jitter of 30 μs. The hypothesis that higher cut-offs would help SFEMGF distinguish between ocular MG and mitochondrial myopathy or oculopharyngeal dystrophy is not supported.

References

1. Keesey JC. Electrodiagnostic approach to defects of neuromuscular transmission. Muscle Nerve 1989; 12: 613-626.
2. Stalberg E, Sanders D. Electrophysiological tests of neuromuscular transmission. *In*: Stalberg E, Young RR, eds. Clinical Neurophysiology. London: Butterworths, 1981: 88-116.
3. Chu JY, Humphrey JG, Bril V. Correlation of clinical status, single-fiber EMG and serum antiacetylcholine receptor antibody in myasthenia gravis [abstract]. Neurology 1984; 34 (Suppl 1): 161.
4. Sanders DB, Howard JF. Single-fiber electromyography in myasthenia gravis. Muscle Nerve 1986; 9: 809-819.
5. Gross PT. Frontalis muscle single fiber electromyography in the evaluation of suspected myasthenia gravis [abstract]. Muscle Nerve 1991; 14: 915.
6. Krendel DA, Sanders DB, Massey JM. Single fiber electromyography in chronic progressive external ophthalmoplegia. Muscle Nerve 1987; 10: 299-302.
7. Fawcett PR, Mastaglia FL, Mechler F. Electrophysiological findings including single fiber EMG in a family with mitochondrial myopathy. J Neurol Sci 1982; 53: 397-410.
8. Roussev R, Ashby P, Basinski A, Sharpe JA. Single fiber EMG in the frontalis muscle in ocular myasthenia: specificity and sensitivity. Muscle Nerve 1992; 15: 399-403.
9. Stalberg E and Trontelj JV. SFEMG findings in different disorders. *In*: Stalberg E and Trontelj JV, eds. Single Fiber Electromyography. Surrey, U.K.: The Mirvalle Press Limited, 1979: 99-150.